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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,672	10/17/2005	Yoshiki Kawabe	KAWABE1	1850

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,672	KAWABE ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,10 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,10 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. In the remarks submitted on 01/09/2008, Applicant amended claims 1, 4, 7, 10, 15 and 16, cancelled claims 9 and 14 and added the new claims 17-22. Thus, claims 1, 4, 7, 10, and 15-22 are pending.

Maintained claim rejections

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 4, 7, 10 and 15-16 remain rejected and the new claims 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Hussain M. (WO/2004/030628, filed on 10/02/2003 with a priority date of 10/02/2002-60/415,091).

Hussain teaches a subpopulation of bone marrow cells which are capable of differentiating into insulin-producing pancreatic islet cells and to a method for treating a diabetic condition by administering adult bone marrow derived stem cells which can differentiate and then function as pancreatic islet cells ([0002]). Also taught is a method

for stimulating the mobilization of cells from bone marrow and the differentiation of bone marrow derived cells into pancreatic islet cells, by treating such bone marrow-derived cells with an effective stimulating amount of granulocyte colony stimulating factor (G-CSF) and/or granulocyte-macrophage colony stimulating factor (GM-CSF). The method may be performed in conjunction with a method for treating a diabetic condition in a mammal, by administering a therapeutically effective amount of bone marrow or an effective subpopulation thereof in combination with purified recombinant G-CSF or GM-CSF in an amount effective to stimulate the mobilization and differentiation of some of the bone marrow cells into pancreatic islet cells ([0010]). The cells used in the method are adult bone marrow cells that have pluripotent differentiation capacity. Such cells, when transplanted, have the potential to restore function of certain endocrine cells to a patient who has lost such production due to disease such as diabetes mellitus. Thus bone marrow derived cells populate pancreatic islets of Langerhans. When purified from islets, said cells express insulin, the glucose transporter 2(GLUT2), and transcription factors typically found in pancreatic beta cells ([0020]). The teachings of Hussain established that bone marrow harbors cells that can differentiate into functionally competent pancreatic endocrine beta cells and thus represent a source for cell-based treatment for diabetes mellitus [(0021] and claims 14-17). The performing of the method for treating and/or preventing a diabetic condition in a mammal in need thereof by administering to the mammal a therapeutically effective amount of autologous or non-autologous bone marrow or an effective subpopulation thereof, wherein the autologous or non-autologous bone marrow, or effective subpopulation thereof, is administered with

purified recombinant G-CSF and/or GM-CSF in an amount effective to stimulate the mobilization and differentiation of some of the bone marrow cells into pancreatic islet cells ([0024]) would necessarily prevent the beta –cell disruption by the inherent properties of the G-CSF administered. Therefore, the teachings of Hussain anticipate the claims 1, 4, 7, 10, and 15-20 of the instant Application.

On page 8 of their remarks, Applicant questioned if Hussain (WO/2004/030628 2003 with a priority date of 10/02/2002-60/415,091) is prior art. The arguments were carefully considered but not found persuasive because the priority date of Hussain is 10/02/2002, which is prior to the priority date of the instant Application.

On page 8 of their remarks, Applicant argues that Hussain is different from the instant Application since, allegedly, it discloses the step of administering bone marrow derived stem cells, whereas the present invention does not comprise administering bone marrow derived stem cells. The arguments were carefully considered but not found persuasive because, as reiterated above in the [0010] paragraph of the Hussain document, a method for stimulating the mobilization of cells from bone marrow and the differentiation of bone marrow derived cells into pancreatic islet cells with an effective stimulating amount of granulocyte colony stimulating factor (G-CSF) and/or granulocyte-macrophage colony stimulating factor (GM-CSF) is clearly taught in the prior art reference. Therefore, the claims 1, 4, 7, 10 and 15-20 are clearly anticipated by Hussain.

New claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The claims contain the wording "promote regeneration" or "provide regeneration" This is a new matter which was not described in the original specification and does not naturally flow from the disclosure of the Application.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 7, 16, 18, 19, 20, 21, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because they contain the wording “colony-stimulating factors as active ingredients”. It is unclear if the factors are active ingredients of a composition or a drug or a pharmaceutical composition. Therefore, the metes and bounds of the claims could not be established.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 4, 7, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamura et al. (JP2001233784, published 08/28/2001).

The claims are drawn to a method for treating diabetes or to regenerate β- cells or to prevent β- cells disruption, which essentially consists of the steps of administering one or more colony-stimulating factors as active ingredients to a diabetic patient in need thereof in an amount sufficient to regenerate or promote regeneration of pancreatic Langerhans' islets of said patient.

Okamura et al. teach a method of treatment which controls the diabetic onset and advance that uses a "promoter of the production of IL-18". The promoter is disclosed to be the macrophage-colony stimulating factor ([0009]-[0012]). The dosages used are presented in the example. It is apparent that the method of treating diabetes using M-CSF was used and the effects of the treatment would have been observed irrespective of the intended use (i.e., by using M-CSF Okamura et al. would already have practiced the invention claimed in the instant application).

8. Claims 1, 4, 7, and 16-20 rejected under 35 U.S.C. 102(b) as being anticipated by Brewitt et al. (U.S. Pat. No. 5,629,286).

Brewitt teaches an effective treatment for insulin-dependent and non-insulin dependent diabetes which will slow the progression of disease and/or relieve disease symptoms by using homeopathic dilutions of granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage-colony stimulating factor (M-CSF) (col. 6, line 37 to col. 7, line 49). By practicing the invention of Brewitt, a person of ordinary skill in the art would have actually practiced the method of the instant application, since the colony stimulating factor would have inherently acted in the manner and having the effects dictated by its structure.

Therefore, the claims 1, 4, 7, and 16-20 are anticipated by Brewitt et al.

9. Claims 1, 4, 7, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Krakowski et al. (J. Pathol. 16, 103-112, 2002).

Krakowski et al. teach a method of treatment of low-dose streptozocin induced diabetes by GM-CSF. Transgenic mice expressing GM-CSF in the pancreas islets were protected from developing streptozocin induced diabetes and from cell disruption (Discussion section). Thus, the teachings of Krakowski et al. anticipate the claims 1, 4, 7, and 16 of the instant Application.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1, 4, 7, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lukic et al. (Develop. Immunol., 6, 119-128, 1998) in view of Dalhoff et al. (J. Inf. Disease., 178, 891-895, 1998).

The claims are drawn to a method for treating diabetes or to regenerate β- cells or to prevent β- cells disruption, which essentially consists of the steps of administering one or more colony-stimulating factors as active ingredients to a diabetic patient in need thereof in an amount sufficient to regenerate or promote regeneration of pancreatic Langerhans' islets of said patient and the colony- stimulating factor is G-CSF.

Lukic et al. teach that the macrophages infiltrate the pancreatic islets in multiple low-dose streptozocin induced diabetes (p. 120, left col. first full paragraph). Also taught is the fact that IL-1 has toxic and destructive effects against β-cells (p.122, right col. last paragraph) The authors teach that treatment with IL-1 inhibitors (such as IL-1 receptor antagonist - IL-1 Ra) suppress development of diabetes (table II; p. 126, concluding comments). Lukic et al. does not teach the use of G-CSF for treatment of diabetes or protecting β-cells.

Dalhoff et al. teach that levels of the IL-1Ra are increased after administration of G-CSF to human patients (abstract).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the G-CSF as taught by Dalhoff et al. to increase the production of IL-Ra as taught by Lukic et al. to treat diabetes by protecting the β- cells with a reasonable expectation of success because by protecting/regenerating the β-cells one would have averted the onset or advancement of diabetes. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

13. Claims 10 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al. (U.S. Pat. No. 6,610,535) in view of Forbes et al. (WO 02/50263, 06/27/2002).

The claims are drawn to a method for producing pancreatic Langerhans β-cells, which comprises the steps of: (a) collecting stem cells after administering one or more colony-stimulating factors to a diabetic patient in need thereof; and (b) differentiating the collected stem cells into pancreatic Langerhans β-cells, wherein the colony-stimulating factor is granulocyte colony- stimulating factor.

Lu et al. teach that Insulin-dependent diabetes mellitus (IDDM) is a good example of a disease that could be cured or ameliorated through the use of stem cells. They teach methods for the isolation and propagation of stem cells from virtually any tissue type. Such stem cells can then be used, for example, for direct transplantation or

to produce differentiated cells in vitro for transplantation of pancreatic and hepatic stem cells that may serve as a source for many other, more differentiated cell types such as pancreatic beta cells (col. 2, line 67 to col.3 line 13). Lu et al. are silent about collecting stem cells from patients pretreated with G-CSF.

Forbes teaches a method of collecting stem cell after administering a composition called mobilizing composition comprising G-CSF (p. 5 lines 7-11). The stem cells are further used in a patient in need of tissue repair as in the case of diabetes mellitus (p. 19, lines 9-17).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the method of obtaining pancreatic beta cells as taught by Lu et al. after collecting the cells as taught by Forbes, to obtain the stem cells needed to be differentiated in Langerhans beta cells with a reasonable expectation of success because both methods have been successfully tested. The motivation to do so would have come from the suggestion of Forbes et al. which showed the benefits of autologous stem cell therapy.

14. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hussain M. (WO/2004/030628) in view of Bonhomme et al. (U.S. Pat. No. 6,303,146).

The claims are drawn to a method for treating diabetes, which comprises the steps of: (a) administering one or more colony-stimulating factors as active ingredients to a diabetic patient and (b) administering to the patient a diabetic drug selected from

the group consisting of sulphonylurea drugs, biguanide drugs and thiazolysine derivative drugs.

The teachings of Hussain were presented supra. Hussain does not address the combination of his method with the administration of sulphonylurea drugs, biguanide drugs and thiazolysine derivative drugs.

Bonhomme et al. teach that oral antidiabetic drugs such as sulphonylureas and biguanidines are established forms of treatment for diabetes either alone or in combination (col. 1, lines 23-32).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the method of Hussain with the method of Bonhomme et al to treat diabetes with a reasonable expectation of success because both methods were established in the art. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tsang et al. (U.S. Pat. No. 6,759,039), Kojima et al. (U.S. Pat. No. 6,232,288), Peck et al. (U.S. Pat. No. 6,001,647), Soria et al. (Diabetes, 49, 1-6, 2000) and Takano et al. (Curr. Pharm. Drugs, 9, 1121-1127, 2003).

Tsang et al. teach culturing techniques for intermediate differentiated pancreatic stem cells that can be propagated in a stable manner in successive serial passaging while maintaining insulin production in response to glucose.

Kojima et al. teach compositions capable of promoting the differentiation of undifferentiated pancreatic cells into insulin-producing beta cells. Methods for treating mammals, including humans, are also provided.

Peck et al. teach methods to grow functional islets in *in vitro* cultures. Also taught are methods that use the in vitro grown islet-like structures for implantation into a mammal for in vivo therapy of diabetes.

Soria et al. teach that insulin secreting cells derived from embryonic stem cells can be used to treat diabetes in Streptozocin- induced diabetic mice.

Takano et al. teach that G-CSF is a key factor in mobilization of stem cell and can also act in differentiation of stem cells.

Conclusion

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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